In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Filed: July 27, 2023

FRANK CRAWFORD,	*	
	*	
Petitioner,	*	No. 18-198V
	*	
v.	*	Special Master Gowen
	*	
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	Entitlement; Influenza ("flu"); Syncopal event.
	*	
Respondent.	*	

Richard Gage, Richard Gage, P.C., Cheyenne, WY, for petitioner.
Emilie Williams, U.S. Dept. of Justice, Washington, D.C., for respondent.

RULING ON ENTITLEMENT[1]

On February 8, 2018, Frank Crawford ("petitioner") filed a petition for compensation in the National Vaccine Injury Compensation Program.[2] Petition (ECF No. 1). Petitioner alleged that the influenza ("flu") vaccine he received on September 6, 2016, caused him to suffer nausea and vomiting, which resulted in him falling and sustaining a head, shoulder, and hip injuries. *Id.*; Petitioner's ("Pet.") Pre-Hearing Brief (ECF No. 78). After a review of the record and an entitlement hearing, petitioner has established by preponderant evidence that he is entitled to compensation.

[1] Pursuant to the E-Government Act of 2002, *see* 44 U.S.C. § 3501 note (2012), because this decision contains a reasoned explanation for the action in this case, I am required to post it to a publicly available website. This decision will appear at https://www.govinfo.gov/app/collection/uscourts/national/cofc or on the Court of Federal Claims website. **This means the decision will be available to anyone with access to the Internet.** Before the decision is posted on the court's website, each party has 14 days to file a motion requesting redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). "An objecting party must provide the court with a proposed redacted version of the decision." *Id.* **If neither party files a motion for redaction within 14 days, the decision will be posted on the court's website without any changes.** *Id.*

[2] The National Vaccine Injury Compensation Program is set forth in Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755, codified as amended, 42 U.S.C. §§ 300aa-10 to 34 (2012) (hereinafter "Vaccine Act" or "the Act"). Hereinafter, individual section references will be to 42 U.S.C. § 300aa of the Act.

I. Procedural History

Petitioner filed his claim for compensation on February 8, 2018, alleging that the high-dose flu vaccine he received on September 6, 2016, caused him to suffer severe nausea, leading to a syncopal event which caused him to fall to the floor and sustain head, shoulder, and hip injuries. Petition at ¶ ¶ 3-5. Petitioner also filed medical records to support his petition. Pet. Exhibits ("Exs.") 1-8.

On March 19, 2019, respondent filed the Rule 4(c) report recommending against compensation. Respondent ("Resp.") Report ("Rept.") (ECF No. 18). Respondent stated that petitioner had failed to provide a medical theory causally connecting the flu vaccine to the onset of his severe nausea that began 48-hours after vaccination and that none of petitioner's treating physicians causally attributed the high-dose flu vaccine to petitioner's nausea which led to his other injuries. *Id.* at 7.

On September 3, 2019, petitioner filed an expert report from Vera Byers MD.[3] Pet. Ex. 13 (ECF No. 36). Medical literature that was cited by Dr. Byers was filed on September 26, 2019. Pet. Exs. 15-16 (ECF No. 39). Respondent filed an expert report from You-Wen He, MD, PhD[4] on March 16, 2020. Resp. Ex. A (ECF No. 43).

The undersigned held a Rule 5 Status Conference on April 27, 2020, where I requested that petitioner file supplemental affidavits to provide additional information about the time period between the flu vaccine and the syncopal event and that the parties should consider litigative risk settlement. Rule 5 Order (ECF No. 45). Further, I instructed petitioner to file a supplemental expert report from Dr. Byers, which would further explain how the high-dose flu vaccine may induce cytokine production that leads to nausea and vomiting.

[3] Dr. Vera Byers received her Ph.D. in immunology in 1969 from the University of California and received her medical degree in 1981 from the University of California at San Francisco. Pet. Ex. 14 at 3. Dr. Byers was in private practice treating patients with allergic and autoimmune diseases, along with cancer from 1984-1987. *Id.* Dr. Byers is board certified in Internal Medicine. *Id.* at 1. She is currently the President of Immunology, Inc., where she has designed and run clinical drug trials for autoimmune diseases, HIV, atopic dermatitis, and certain types of cancers. *Id.* at 1-2. Dr. Byers has served on the editorial board for Cancer Immunology and Immunotherapy and Cancer Drugs. *Id.* at 4. She had been an adjunct professor of immunodermatology at the University of California San Francisco. *Id.* at 5. Dr. Byers has co-authored numerous medical articles in peer reviewed journals. *Id.* at 8-19. She has testified as an expert in immunology in other cases in the Vaccine Program and I admitted her as an expert in immunology. *See* Tr. 66.

[4] Dr. You-Wen He received his medical degree in 1989 from the Institute of Microbiology and Epidemiology in Beijing. Resp. Ex. B. He went to the University of Miami School of Medicine in Miami, Florida for his Ph.D. *Id.* at 1. Dr. He is currently serving as a Professor of Immunology at Duke University Medical Center. *Id.* at 1. Prior to joining the faculty at Duke University, Dr. He was a senior fellow at the Howard Hughes Medical Institute, Department of Immunology at the University of Washington. *Id.* at 1. Dr. He is currently a reviewer of multiple medical journals and publications. *Id.* at 2. Dr. He is currently performing research in the field of immunology and cancer. *Id.* at 5. He has been the lead author or co-author in many medical publications in the field of immunology. *Id.* at 10-18. During the hearing, Dr. He testified that he has testified in three other Vaccine Program cases. Tr. 113. Dr. He was admitted as an expert in the field of immunology during the hearing. *Id.*

Petitioner filed a supplemental affidavit on June 1, 2020. Pet. Ex. 17 (ECF No. 46). On August 21, 2020, petitioner filed a supplemental expert report from Dr. Byers, along with two additional medical articles to support her opinion. Pet. Exs. 18-20 (ECF No. 52).

Another status conference was held on September 25, 2020, where the undersigned explained that the case would be referred to Alternative Dispute Resolution ("ADR"). Respondent filed a status report on October 9, 2020 stating that he was interested in participating in ADR, but would also file a supplemental responsive expert repot from Dr. He. Resp. Status Rept. (ECF No. 54). Respondent filed a supplemental expert report from Dr. He on November 4, 2020. Resp. Ex. C (ECF No. 57).

Unsuccessful in ADR, an entitlement hearing was set for April 14-15, 2021. Hearing Order (ECF No. 68). Petitioner filed a third expert report from Dr. Byers on March 26, 2021. Pet. Ex. 21 (ECF No. 64). Respondent also filed a third expert report from Dr. He on June 28, 2021. Resp. Ex. D.

Both parties submitted pre-hearing briefs prior to an entitlement hearing. Pet. Pre-Hearing Brief (ECF No. 78); Resp. Pre-Hearing Brief (ECF No. 80). An entitlement hearing was held on April 14, 2021 via remote teleconference. After the entitlement hearing, the case was referred back to ADR before Chief Special Master Corcoran. Order Referring Case to ADR (ECF No. 93).

The parties entered into a 15-week stipulation order after ADR concluded. ECF No. 98. However, on November 28, 2022, respondent filed a status report stating that "the authorized representative of the Attorney General has declined to grant settlement authority for the proposed tentative settlement in this case," and respondent requested that the Court proceed with a ruling on entitlement. Resp. Status Rept. (ECF No. 99).

The parties submitted post-hearing briefs. *See* Resp. Post-Hearing Brief ("Resp. Brief"); Pet. Post-Hearing Brief ("Pet. Brief"). Both parties discussed the issue of entitlement and damages in their briefs.[5] This matter is now ripe for adjudication.

II. Legal Standard for Entitlement

A petitioner may prevail by proving either that (1) the vaccinee suffered an injury listed on the Vaccine Injury Table with onset beginning within a corresponding time period following receipt of a corresponding vaccine (a "Table Injury"), for which causation is presumed or that (2) the vaccinee suffered an injury that was actually caused by a vaccine. Under either method, however, the petitioner must also show that the vaccinee "suffered the residual effects or complications of the illness, disability, injury, or condition for more than six months after the administration of the vaccine." Section 11(c)(1)(D)(i).

In the present case, petitioner does not allege a Table injury. Thus, he bears the burden of establishing actual causation. To do so, he must "show by preponderant evidence that the vaccination brought about the injury by providing 1) a medical theory connecting the vaccination

[5] A ruling on damages will be filed separately.

and injury; 2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and 3) a showing of a proximate temporal relationship between vaccination and the injury." *Althen v. Sec'y of Health & Human Servs.,* 418 F. 3d 1274, 1278 (Fed. Cir. 2005). There must be preponderant evidence for each *Althen* prong. *Caves v. Sec'y of Health & Human Servs.,* 100 Fed. Cl. 119, 132 (2011), *aff. per curiam,* 463 Fed. Appx. 932 (Fed. Cir. 2012).

Under *Althen* prong one, the causation theory must relate to the injury alleged. Thus, a petitioner must provide a "reputable" medical or scientific explanation that the vaccine received *can cause* the type of injury alleged. *Pafford*, 451 F.3d at 1355-56. The theory must be based on a "sound and reliable medical or scientific explanation." *Knudsen*, 35 F.3d at 548. It must only be "legally probable, not medically or scientifically certain." *Id*. at 549. However, the theory still must be based on a "sound and reliable medical or scientific explanation." *Id*. at 548. The Federal Circuit explained in *Althen* that "while [that petitioner's claim] involves the possible link between [tetanus toxoid] vaccination and central nervous system injury, *a sequence hitherto unproven in medicine*, the purpose of the Vaccine Act's preponderance standard is to allow the finding of causation in a field *bereft of complete and direct proof of how vaccines affect the human body." Althen,* 418 F.3d at 1280 (emphasis added).

Under *Althen* prong two, petitioner must prove "a logical sequence of cause and effect showing that the vaccination was the reason for [her] injury." *Althen*, 418 F.3d at 1278. This prong is sometimes referred to as the "did it cause" test; i.e. in this particular case, did the vaccine(s) cause the alleged injury. *Broekelschen,* 618 F. 3d at 1345 ("Because causation is relative to the injury, a petitioner must provide a reputable medical or scientific explanation that pertains specifically to the petitioner's case"). Temporal association alone is not evidence of causation. *See Grant v. Sec'y of Health & Human Servs.,* 9556 F.2d 1144, 1148 (Fed. Cir. 1992). This sequence of cause and effect is usually supported by facts derived from petitioner's medical records. *Althen,* 418 F.3d at 1278; *Andreu,* 569 F.3d at 1375-77; *Capizzano,* 440 F.3d at 1326; *Grant,* 956 F.2d at 1148.

Althen prong three requires establishing a "proximate temporal relationship" between the vaccination and the injury alleged. *Althen* at 1281. That term has equated to the phrase "medically-acceptable temporal relationship." *Id*. A petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation." *de Bazan v. Sec'y of Health & Human Servs.,* 539 F.3d 1347, 1352 (Fed. Cir. 2008). The explanation for what is medically acceptable timeframe must align with the theory of how the relevant vaccine can cause an injury (*Althen* prong one). *Id*. at 1352.

The preponderance of the evidence standard requires the petitioner to demonstrate that it is "more likely than not" that the vaccine caused the injury. *Moberly v. Sec'y of Health & Human Servs.,* 592 F.3d 1315, 1322 n.2 (Fed. Cir. 2010). Proof of medical certainty is not required. *Bunting v. Sec'y of Health & Human Servs.,* 931 F.2d 867, 873 (Fed. Cir. 1991). A petitioner must demonstrate that the vaccine was "not only [a] but for cause of the injury but also a substantial factor in bringing about the injury." *Moberly*, 592 F.3d at 1321 (quoting *Shyface v. Sec'y of Health & Human Servs.,* 135 F.3d 1344, 1352-53 (Fed. Cir. 1999); *Pafford v. Sec'y of Health and Human Servs.*, 451 F.3d 1352, 1355 (Fed. Cir. 2006). Causation is determined on a

case-by-case basis, with "no hard and fast *per se* scientific or medical rules." *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 548 (Fed. Cir. 1994). A fact-finder may rely upon "circumstantial evidence" which is consistent with the "system created by Congress, in which close calls regarding causation are resolved in favor of injured claimants." *Althen*, 418 F. 3d at 1280.

The petitioner often presents expert testimony in support of his or her claim. *Lampe v. Sec'y of Health & Human Servs.*, 219 F.3d 1357, 1361 (Fed. Cir. 2000). Expert testimony in the Vaccine Program may be evaluated according to the factors set forth in *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 594-96 (1993); *see also Cedillo*, 617 F.3d at 1339 (citing *Terran v. Sec'y of Health & Human Servs.*, 195 F.3d 1302, 1316 (Fed. Cir. 1999). A special master may use the *Daubert* framework to evaluate the reliability of expert testimony, but expert testimony need not meet each *Daubert* factor to be reliable. *Boatmon v. Sec'y of Health & Human Servs.*, 941 F.3d 1351 (Fed. Cir. 2019). The *Daubert* factors are "meant to be helpful, not definitive," and all factors "'do not…necessarily apply even in every instance in which the reliability of scientific testimony is challenged.'" *Boatmon*, 941 F. 3d at 1359 (citing *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 151, 119 S. Ct. 1167, 143 L.Ed.2d 238 (1999). Thus, for Vaccine Act claims, a "special master is entitled to require some indicia of reliability to support the assertion of the expert witness." *Moberly* at 1324. Where both sides offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their competing theories." *Broekelschen v. Sec'y of Health & Human Servs.*, 219 F.3d 1339, 1347 (Fed. Cir. 2010) (citing *Lampe*, 219 F.3d 1357 at 1362).

If the petitioner makes a *prima facie* case supporting vaccine causation-in-fact, the burden shifts to respondent to show by a preponderance of the evidence that the injury is instead due to factors unrelated to the administration of the vaccine. *Deribeaux v. Sec'y of Health & Human Servs.*, 717 F.3d 1363, 1367 (Fed. Cir. 2013) (citing Section 13(a)(1)(B)). Respondent has the burden of demonstrating that: "[A] factor unrelated to the vaccination is the more likely or principal cause of injury alleged. Such a showing establishes that the factor unrelated, not the vaccination, was 'principally responsible' for the injury. If the evidence or alternative cause is seen in equipoise, then the government has failed in its burden of persuasion and compensation must be awarded." *Knudsen*, 35 F.3d at 551.

III. Ruling on Entitlement

A. Evidence submitted

1. Summary of petitioner's medical records

Petitioner was an 84-year-old part-time orthodontist when he received the flu vaccine on Monday, September 6, 2016. Pet. Ex. 2 at 72; Transcript ("Tr.") 8. Petitioner also had his right leg amputated above the knee some years before. Tr. 10. Prior to his vaccination, petitioner was treated for gastric ulcers, which had healed. Pet. Ex. 2 at 60.

Petitioner received the high-dose flu vaccine in the late afternoon of September 6, 2016. Tr. 8; Pet. Ex. 1 at 1-2. He testified that his wife got the high-dose flu shot at the same time.

Pet. Affidavit ("Aff.") at ¶¶ 3-4. He stated that approximately one hour after the vaccination, he and his wife began to get "very ill." Tr. 9. Petitioner testified that they both experienced nausea, were vomiting, and retching. *Id*. He stated that he went to bed without eating dinner. *Id*.

The next day, September 7, 2016, petitioner stated that he felt worse, experiencing nausea, and still vomiting. Tr. 9. He testified that his wife was also still ill, and they both stayed in bed both days. *Id*. at 10.

On September 8, 2016, petitioner stated that he had gone into the bathroom using his wheelchair and he had retched so hard that he fainted and fell out of his wheelchair. Tr. 10; Pet. Aff. at ¶ 4. Petitioner stated that when he woke-up he was covered in blood from a cut from his head. Tr. 10. Emergency medical personnel were called to petitioner's house for "an 84-year-old who had fallen out of his wheelchair, striking his head on the toilet." Pet. Ex. 3 at 1. According to the EMS report, petitioner reported:

> He and his wife went to get a flu shot yesterday, and that his nausea started after he was given the shot. He admitted that he got up to go the bathroom, he was not able to go, and after he got back into his wheelchair, he began to wretch really hard, passing out, and waking up on the floor.

Id. Petitioner had a 2 cm laceration on his forehead. *Id*. Petitioner reported that he continued to feel nauseous but had felt better laying down on the bathroom floor. *Id*. EMS administered Zofran to petitioner to treat the nausea. Petitioner was transported to Texas Health Huguley emergency department for additional treatment. During the hearing, petitioner testified that he did not "recall the ambulance ride." Tr. 12.

Under the History of Present Illness taken at the emergency department of Huguley Hospital, it was recorded that petitioner had fallen approximately one hour ago and that he had a laceration on his left forehead. Pet. Ex. 4 at 148. Additionally, under neurologic symptoms it was noted that petitioner had "altered level of consciousness." *Id*. Petitioner stated that he did not remember going into the emergency room and he did not remember what happened while he was in the emergency room. Tr. 12. He testified that he was not admitted when he was evaluated in the emergency room. *Id*. at 13. A CT and MRI of petitioner's brain and head were ordered. Pet. Ex. 4 at 151. According to the emergency room records, at approximately 1:36 pm, petitioner was being discharged and it was recommended that petitioner follow-up with his primary care physician. *Id*.

Petitioner was discharged from the emergency room and his wife took him by wheelchair to their car. Tr. 13; Pet. Ex. 4 at 151. A nurse was with him and his wife, presumably to assist her lifting him into the car. Pet. Ex. 4 at 151. Petitioner testified that he was in a tremendous amount of pain from his shoulder and "during the process of getting into the car and sitting down," he experienced pain in his shoulder when pushing down on the arms of the wheelchair. Tr. 14. Petitioner testified that the pain was so intense he passed out. *Id*.

Petitioner's wife took him back into the emergency room for "seizure-like activity." Pet. Ex. 4 at 151. The nurse that was assisting petitioner and his wife also had visualized the episode.

Id. Petitioner was admitted for further monitoring and tests. Dr. Cryus Allan Manoucheri examined the petitioner and wrote that petitioner was moaning and complaining of left shoulder pain and right leg pain during the physical examination. *Id*. at 143. Dr. Manoucheri recounted petitioner's history and wrote:

> The patient is an 84-year-old man who 1 hour prior to arrival in the ER had a fall from the toilet for what sounded like vasovagal syncope spell. He fell and hit his head and lost consciousness for an unknown duration. He had blood coming from his left forehead and from his gums. So, his wife brought him to the emergency room for evaluation. The patient was evaluated in the ER, was cleared, and was discharged home; however, while en route to the car, the patient had what sounds like a simple partial seizure. Thus, he was brought back to the ER….According to the emergency room physician, the patient had some postictal confusion after the initial seizure. The patient was admitted. Prior to my initial evaluation….patient had a second seizure what sounds like a simple partial seizure for which he did not lose consciousness, and according to the nursing staff, he did not have any postictal confusion.

Pet. Ex. 4 at 143. Dr. Manoucheri observed that petitioner was "positive for seizures," and was complaining of right leg pain and left shoulder pain. *Id*. at 144. He diagnosed petitioner with "new onset seizures, secondary to posttraumatic head injury," and "left shoulder pain, secondary to possible contusion after fall." *Id*. at 145. An X-ray for petitioner's left shoulder was ordered and petitioner was started in Keppra and gabapentin. *Id*.

Later that day, petitioner was examined by orthopedist Dr. Jeffry Ratusznik. Pet. Ex. 4 at 172. Dr. Ratusznik noted that the X-ray of petitioner's shoulder revealed a "closed left proximal humerus fracture dislocation." *Id*. He noted that "On examination, [petitioner] complains of pain localized to the left shoulder. He denies any numbness, paresthesias, radicular pain, or subjective weakness in the distal left upper extremity. Pain has been relatively well controlled at rest, but severe with any attempts at shoulder range of motion." *Id*. Petitioner had moderate swelling on his left shoulder. *Id*. at 174. The assessment was "closed, comminuted left proximal humerus fracture dislocation," and the plan was for an "open reduction and internal fixation" once petitioner was cleared by neurology for general anesthetic. *Id*. On September 11, 2016, petitioner underwent a "left shoulder proximal humerus reverse shoulder replacement." Pet. Ex. 4 at 222-23.

Petitioner was discharged from Huguley Hospital on September 13, 2016 to Baylor Institute Rehabilitation Center. Pet. Ex. 4 at 140. Petitioner's discharge diagnosis included, "seizure, likely post-concussion; vasovagal syncope, resolved; left shoulder acute comminuted displaced proximal left humeral fracture status-post shoulder arthroplasty…The patient is being discharged to rehab, acute." *Id*. The discharge summary also stated that petitioner "is an 84-year-old gentleman who came to the hospital after he had a vasovagal syncope and he had head trauma. Subsequently, he experienced a few seizures, felt to be post-concussion seizures. He was also found to have a left shoulder fracture for which he underwent left shoulder proximal humerus reverse shoulder replacement by Dr. Bajaj." *Id*. at 141.

While he was at the Baylor Institute Rehabilitation Facility, on September 14, 2016, petitioner experienced another change in his neurological status and he was taken to Texas Health Harris Methodist Hospital in Forth Worth, Texas. *See* Pet. Ex. 8 at 20; Pet. Ex. 2 at 72.

On October 10, 2016, petitioner had a follow-up appointment with Dr. Gurpreet Bajaj. Pet. Ex. 2 at 83. Dr. Bajaj observed that petitioner was able to stop using an arm sling and was moving his left arm well. *Id*. Further, Dr. Bajaj stated that petitioner would be able to use that arm with a walker and while trying to do therapy for his pelvic fracture. *Id*. Petitioner had normal range of motion, normal flexion, extension and rotations upon examination and normal strength. *Id*. at 84. Dr. Bajaj ordered petitioner to physical therapy for his left shoulder. *Id*.

Petitioner had an initial evaluation for physical therapy on October 12, 2016 at the Hugley Hospital Fort Worth South campus. Pet. Ex. 4 at 27. Petitioner reported that his shoulder pain was a 2/10 and it ranges from not hurting to an 8/10. *Id*. Petitioner described the pain as "stabbing" and also "intermittent." *Id*. Under "History," the record states, "Patient is an 84 y/o male who presents to PT clinic s/p [left] reverse TSA on 9/11/2016. Patient sustained left shoulder injury and right pelvic fracture on 09/06/2016 after a fall. Patient reports that he was getting up from the toilet and that he had been suffering from illness after the flu shot which triggered the fall." *Id*. The initial physical exam showed that petitioner had decreased range of motion in his left shoulder compared to his right and decreased strength. *Id*. at 28. Petitioner began physical therapy twice a week for six weeks. *Id*. at 29.

Petitioner had a hospital follow-up with his primary care physician, Dr. Bates on October 11, 2016. Pet. Ex. 2 at 89. The "History of Present Illness" from this encounter provides, "Complaint #1: hospital follow-up. Had fracture right hip left shoulder. [T]his was after syncope when he was ill on toilet; has had rehab and surgery doing a lot better." *Id*. Dr. Bates recorded that "pt passed out and hit his head, pt had flu shot previously," and "pt went to ER on 09/08/2016 for fall." *Id*.

Petitioner had another follow-up with Dr. Bajaj for his left shoulder on November 7, 2016. Pet. Ex. 6 at 11. Petitioner reported that his pain was a 0/10 and that he had been "pain free for awhile." *Id*. Petitioner also told Dr. Bajaj that he was returning to work on November 10, 2016. *Id*. Additionally, petitioner informed Dr. Bajaj that he was not feeling much pain in his hip anymore and he is participating in physical therapy at Huguley Fitness Center. *Id*. Further, petitioner stated that he was not taking any pain medication. Dr. Bajaj performed a physical examination of petitioner's left shoulder where petitioner demonstrated normal strength and normal range of motion. *Id*. Dr. Bajaj released petitioner to go back to work and recommended that he continue physical therapy to continue to strengthen his left shoulder. *Id*. at 11-12.

On December 30, 2016, petitioner was discharged from physical therapy at Texas Huguley Health. Pet. Ex. 4 at 20. Petitioner reported that his pain was a 0/10 at discharge but did experience pain at 6/10 during the week. *Id*. at 21. Additionally, petitioner reported that he was looking forward to returning to work. *Id*. It was recommended that petitioner continue physical therapy twice a week for another two weeks. *Id*.

2. Petitioner's statements

Petitioner submitted two affidavits and testified at the entitlement hearing. He stated that he remembered getting the flu shot on Monday, September 6, 2016. Tr. 6; Pet. 12 at ¶ 3; Pet. Ex. 17 at ¶ 2. He stated that the vaccination appointment was in the afternoon, at approximately 4:00 pm. Pet. Ex. 17 at ¶ 2; Tr. 8. Him and his wife got the flu shot on the same day. *Id*. Petitioner testified that he was feeling healthy when he went to get his flu shot. Tr. 24.

Petitioner stated that both he and his wife began to feel ill about one hour after vaccination. Tr. 9; Pet. Ex. 12 at ¶ 4. He stated that he began to feel nauseous and had episodes of "retching." *Id*. He stated that he also experienced fatigue and malaise, which continued to worsen throughout the evening and into September 7, 2016. Pet. Ex. 17 at ¶ 3. During the hearing, he explained that he and his wife stayed in bed most of the day on September 7, 2016. Tr. 10. He stated that he and his wife felt "a little temperature," but nothing "severe." Tr. 10. This is consistent with his affidavit, where petitioner stated that he developed a low-grade fever following the vaccination. Pet. Ex. 12 at ¶ 4.

The next day, September 8, 2016, petitioner stated that he had "no improvement" and he was doing a lot of "retching," and was experiencing a lot of nausea. *Id*. He testified that he went to the bathroom in his wheelchair at approximately 10:30 AM and he was retching, when he fell out of his wheelchair. Tr. 10-11. He testified that he did not remember falling out of the wheelchair, but when he woke up, he was covered in blood. *Id*. He stated that he had a cut on his forehead and had severe pain in his shoulder and right hip. Tr. 10-11. Petitioner testified that his wife called an ambulance. Tr. 11.

He stated that did he not remember much of the ride in the ambulance to the hospital and that he does not remember going to the emergency department at Texas Huguley Hospital. Tr. 11-12. Petitioner testified that he was not admitted to the hospital and his wife took him via wheelchair out to the car when he was discharged. Tr. 13. He testified that he was in a tremendous amount of pain in his shoulder and "during the process of getting into the car and sitting down, there was pain when I pushed down on the arms of my wheelchair, and it was so severe that I passed out again." Tr. 14. He explained that while he does not recall this time period, his wife explained to him what had happened. *Id*. Petitioner testified that his wife took him back into the hospital where they admitted him. Tr. 16.

Petitioner stated that his wife told the x-ray technician to take an x-ray of his left shoulder. Tr. 16. Petitioner stated that later an x-ray of his back and pelvis were taken, which identified a fractured pelvis and a fracture of his L1 vertebrae. Tr. 17.

Petitioner explained that initially the pain in his left shoulder was the "worst pain" that he had ever experienced. Tr. 18. He testified that his surgeon was able to repair the injury and he was able to resume the use of his left arm after physical therapy. Tr. 19. However, petitioner stated that he does not have much strength in his left arm, and he gets periodic numbness in his left hand. *Id*. He testified that his pelvic fracture healed, and he had no residual pain or issues with it. Further, petitioner stated that his L1 vertebrae was painful at first but healed "fine" and he does not experience any residual deficits or pain. Tr. 21.

Petitioner testified that he was unable to work until he had completed physical therapy. Tr. 22. He stated that it was several months after his accident when he was able to return to work, and he worked several more years before retiring at 86.

3. Statement of Dr. Edward Bates

Petitioner's treating primary care physician wrote a letter for petitioner. Pet. Ex. 10. In the letter, Dr. Bates wrote:

> [Petitioner], DOB 03/19/1932 is a current patient of Dr. Edward Bates. The patient had a vaso-vagal adverse reaction to the influenza vaccine in 201[6]. The Vaso-Vagal syndrome caused dizziness and affected gait of the patient causing the patient to fall. The fall caused several injuries for the patient.

Id. Dr. Bates also testified at the entitlement hearing. During the hearing, Dr. Bates testified that he had been treating the petitioner since 2015. Tr. 32. He stated that petitioner, for his age, was generally healthy prior to September 2016. *Id*. Dr. Bates stated that petitioner had some blood pressure issues and previously had his right leg amputated. *Id*.

Dr. Bates acknowledged that petitioner had been previously hospitalized for a blood clot in 1995 and again in 2009 and had been treated for stomach ulcers which had healed with Protonix. Dr. Bate testified that petitioner had a prior pelvic scan which showed asymptomatic diverticulosis but not diverticulitis. Tr. 34-35. He testified that "probably half the people in the country have that." *Id*. He testified that prior to September 2016, petitioner was on multiple medications, but that petitioner never complained of nausea or dizziness from those medications. Tr. 57. Dr. Bates testified that if the medications were causing those side effects he would discontinue or change them. *Id*.

After reviewing petitioner's hospital course, Dr. Bates testified that the first time he saw the petitioner following the hospitalization was on October 11, 2016. Tr. 46.

When Dr. Bates was asked about what he meant by the word "vasovagal" in his letter, he testified that "when the vagal nerve gets very stimulated, and that can be from…fear, shock, pain, sometimes physical things, the nerve makes the heart slow down and so vasovagal would either mean….your heart was going very slow or they pass out." Tr. 51. He clarified that while he did not use the word "syncope" in his letter he meant "light-headedness and/or fainting." Tr. 52. He testified that he was trying to "indicate the faintness or either [petitioner's] passing out or close to passing out made him fall." *Id*. Dr. Bates was asked, "Do you believe that was due to his flu vaccine," and he responded, "I do." *Id*. He testified that "it's not unusual" that his patients experience nausea and vomiting after receiving the high-dose flu vaccine. *Id*. Dr. Bates testified that the onset of those symptoms occurs "usually a few hours after the vaccine," and can last for two to three days. Tr. 53. Dr. Bates stated that dizziness or syncope after the high-dose flu vaccine is a less common side effect and that the petitioner "may be the only person I know who actually passed out." *Id*. When Dr. Bates was asked by the Court, "Do you believe that the vasovagal attack or the fainting was directly caused by the nausea and retching that he was

having," Dr. Bates responded, "I do." Tr. 58. Dr. Bates testified that petitioner never had complaints of light-headedness or dizziness before and with the timing of the flu shot "and then to go [get] sick pretty quickly, the timing of it makes me think that [the flu shot] is what caused it." Tr. 59.

4. Petitioner's expert's opinion on vaccine causation

Dr. Vera Byers wrote three expert reports to support vaccine causation, and she testified at the entitlement hearing. Pet. Exs. 13, 18, 21. Dr. Byers opined that the high-dose influenza vaccine petitioner received on September 6, 2016 initiated his nausea and retching, caused by cytokines released from the innate immune system reacting to the vaccine. Pet. Ex. 13 at 2.

Dr. Byers testified that the high-dose flu vaccine, administered to those 65-years and older, contains four times the dose of each antigen compared to the Fluzone. Tr. 69. She stated that the high-dose flu vaccine can cause malaise, nausea, vomiting and fever. *Id.* at 70. Dr. Byers, referencing the package insert of the Fluzone High Dose, observed that nausea, vomiting, and fatigue have all been reported as "Post Approval Events." Pet. Ex. 13 at 2; Tr. 74. The Fluzone High Dose package insert contains information about post-marketing events reported after the Fluzone High-Dose had been approved. Pet. Ex. 9 at 7.[6] The package insert provides that "gastrointestinal disorders: nausea, diarrhea," have been reported for the Fluzone High-Dose. *Id.* at 8. Dr. Byers also observed that the Centers for Disease Control and Prevention ("CDC") provides safety information for each vaccine, including the flu vaccine. Tr. 73; *see* Pet. Ex. 16.[7] Dr. Byers testified that the fact sheet approved by the CDC, which is given to patients to show which common side effects they may experience. Tr. 73. She stated that the fact sheet indicates that common side effects include "soreness, redness, and swelling from the shot….headache, common; fever, common; nausea, pretty common; and myalgias (muscle aches)." *Id.*; Pet. Ex. 16.

Dr. Byers opined that petitioner suffered from a syncopal event after receiving the high-dose flu vaccine. Tr. 74. She stated that a vasovagal faint is when "there is a transient dilation of…many of the peripheral vessels which then drains the blood from the brain," which causes fainting because the brain has lost blood. *Id.* She described a vasovagal event as "transient." *Id.* Dr. Byers opined that petitioner's vasovagal event, which included symptoms of nausea, was caused by the cytokines released by the immune system in reaction to the flu antigens. Pet. Ex. 13 at 2; Tr. 75. According to Dr. Byers, "there was a defective regulation of the cytokines," and "when they were supposed to be turned off or calmed down, it just didn't turn off and the cytokines continued to flood the system, producing the faint." Tr. 75.

Dr. Byers testified that anti-inflammatory cytokines, such as IL-10 are triggered at the same time that a vaccine is given. Tr. 82. She stated, "initially all of the pro-inflammatory cytokines pop-up and the macrophages and monocytes grab the antigen with the toll-like

[6] Sanofi Pasteur 372 Fluzone High-Dose, Highlights of Prescribing Information (2016). [Pet. Ex. 9].

[7] Centers for Disease Control and Prevention (CDC), Influenza (Flu), Flu Vaccine Safety Information (2019). [Pet. Ex. 16].

receptors, and present it to the T cells. But at the same time, [a person] has a built-in reaction that will damp this response down if it keeps being too intense, and that is not happening with the influenza vaccine." Tr. 82; Pet. Ex. 18. In her third report, she stated that "the immediate reaction [to a vaccine] is mediated by pro-inflammatory cytokines such as TNF-α and IL-6. This process must be tightly controlled in order to limit self-induced damage. This is done by the induction of anti-inflammatory cytokines such as IL-10 which clamps down inflammation." Pet. Ex. 24 at 2.

Dr. Byers referenced the paper by *Mohanty*, which examined inflammatory monocyte levels post-influenza vaccination in older and younger populations. *See* Pet. Ex. 19.[8] The researchers measured monocyte levels in older and younger patients at day 2, day 7 and day 28. *Id.* at 4. They found that CD14+ and CD16+ inflammatory monocytes increased on days 2 and 7 after vaccination and returned to baseline on day 28 in both older and younger populations. *Id.* at 8. Further, the authors found that some older subject had a four-fold increase in antibody responses to the influenza vaccine, deemed "responders," while other older subjects did not (non-responders). Importantly, the "older responders to the vaccine had increased levels of TNF-α and IL-6 in both monocyte populations on days 2, 7 and 28. *Id.* at 9. The authors of *Mohanty* also observed that levels of IL-10 in older populations is *generally* elevated. *Id.* at 7. Importantly, the authors found that CD14 and CD16 monocytes and IL-10 levels remained stable between days 0 and 2 before increasing at days 7 and 28. *Id.* at 7. Further, the authors found that those older "non-responder" patients had significant increases of IL-10 compared to their responder counter parts. *Id.* In other words, the older "responders" demonstrated an early increase in the inflammatory cytokine TNF-α but not the same level of regulatory IL-10 cytokines as did the non-responders.

Dr. Byers stated that petitioner would classify as a "responder" in the *Mohanty* article, based on his report of nausea and vomiting and by his laboratory results which demonstrated elevated monocytes when he was in the hospital on September 8-two days post-vaccination. Pet. Ex. 24 at 3; *see also* Pet. Ex. 4 at 150 (petitioner's monocyte level was recorded as 13.3% "HI."). She testified that the monocyte cells express toll-like receptors, which will stimulate T cells to produce cytokines. Tr. 89. She stated that because petitioner's monocytes were elevated there would likely be an increase in production of inflammatory cytokines. Tr. 91. Dr. Byers stated that the petitioner's elevated monocytes were caused by the flu vaccine he had received two days earlier and nothing in the record suggests an alternative cause. She testified that monocytes being elevated a few days post-vaccination and then dropping, as was the case of petitioner's monocyte levels, consistent with the immune suppressor cells being activated at that later time. Tr. 93.

Dr. Byers testified that the onset of petitioner's nausea, occurring within one hour of vaccination and remaining elevated is consistent with the rapid activation of cytokines and the delayed response of suppressor cytokines. Dr. Byers referenced an article by *Chatziandreou et al.*, which examined how macrophages can initiate a cytokine storm after an inactivated influenza vaccination to support her opinion that cytokines are rapidly produced post-influenza

[8] Mohanty, S., et al, *Prolonged Proinflammatory Cytokine Production in Monocytes Modulated by Interleukin 10 After Ianfluenza Vaccination in Older Adults,* J. of Infectious Diseases 1174-84 (2015). [Pet. Ex. 19].

vaccination. Pet. Ex. 23.[9] The authors of this study vaccinated mice with the inactivated influenza vaccine and then measured the expression of different proinflammatory cytokines. *Id.* at 5. They found "a rapid and significant secretion of IL-1α and IFN-β in the lymph node within the first 90 minutes," post-vaccination. *Id.* Dr. Byers also observed that the Vaccine Injury Table has "vasovagal syncope" listed following the seasonal flu vaccine, which identifies symptoms of nausea and lightheadedness as symptoms that may precede the fainting event. Pet. Ex. 13 at 2. On the Vaccine Injury Table, the appropriate timeframe for the vasovagal event to occur is equal to or less than one hour after vaccine administration. *Id.* She stated that the petitioner testified that within one-hour of the vaccine he was feeling ill and nauseous, consistent with the symptoms described in the Vaccine Table. Additionally, Dr. Byers testified that the high-dose Fluzone package insert records "malaise" as a systemic adverse event that occurred within three days after vaccination. Tr. 97. The package insert provides that 18% of recipients of the high-dose flu vaccine reported "malaise" as a systemic adverse event within 7 days of vaccination, which was higher than those who received the regular flu vaccine. Pet. Ex. 9 at 6. In fact, all systemic adverse events reported post-vaccination for the high-dose flu vaccine were higher compared to the regular flu vaccine. *Id.* Dr. Byers testified that petitioner's symptoms of malaise with vomiting was consistent with the reports of systemic adverse events recorded in high-dose flu vaccine package insert. Tr. 97.

Dr. Byers concluded that the high-dose flu vaccine petitioner received on September 6, 2016, caused a dysregulated cytokine release process, leading to his vasovagal event that occurred on September 8, 2016. Tr. 99, 108.

5. Respondent's expert's opinion on vaccine causation

Respondent's expert, Dr. He also submitted three expert reports and testified during the entitlement hearing. Resp. Exs. A-D. Dr. He opined that petitioner's nausea, which led to his fainting and subsequent hospitalization, was caused by petitioner's pre-existing gastrointestinal issues. Resp. Ex. A at 4. Further, Dr. He acknowledged that the seasonal influenza vaccine may cause nausea and it is in the package insert, but that the package insert does not give the timing of the onset of nausea after vaccination. *Id.* During the hearing, Dr. He testified that "basically all vaccinations will cause nausea," and the timing of the petitioner's nausea is the determinative factor as to whether it is related to the vaccination at issue. Tr. 115. Apparently referencing the Vaccine Injury Table's listing for vasovagal syncope and the onset of nausea within one hour of vaccination, he stated, "it's not really immune-mediated….because it's within one hour of vaccination, I think it's generally…related to….nerve reaction….It's not because of rapid, acute immune response that's within one hour." Tr. 116. Dr. He was asked by the Court if he agreed whether vaccines can cause nausea and vomiting and he stated, "Absolutely. A lot of vaccines will do that, but it's rapid response, like within an hour, people can faint after vaccination." Tr. 116-17. However, Dr. He opined that a reaction within the hour is not because of an immunological response. Tr. 149.

[9] Chatziandreou, N. et al., *Macrophage Death following Influenza Vaccination Initiates the Inflammatory Response that Promotes Dendritic Cell Function in the Draining Lymph Nodes*, 18 Cell Reports 2427-2440 (2017). [Pet. Ex. 23].

During the hearing, Dr. He argued that petitioner did not have an abnormal cytokine response to the high-dose flu vaccine. Tr. 119. He testified that it could be "a remote possibility" that a "normal cytokine response to the high-dose flu vaccine" could have caused petitioner's nausea and vomiting. Tr. 120. Initially, Dr. He asserted that petitioner's monocyte levels were not increased two days after the vaccination at issue, but later re-read petitioner's medical records and noted that petitioner had elevated monocytes on September 8, 2016, two days post-vaccination. Tr. 123. Dr. He stated that monocytes release inflammatory cytokines and petitioner's elevated monocytes do not represent a "dysregulated cytokine function." Tr. 124. Instead, he argued that the petitioner's elevated monocytes were evidence that the innate immune system was responding appropriately to the high-dose flu vaccine, which is how all vaccines work. Resp. Ex. C at 4. He wrote, "Fluzone High-Dose vaccine will cause innate immune system response by activating innate immune cells including monocytes, macrophages, neutrophils, and dendritic cells, and release of cytokines including IL-1, IL-6, IFN-γ, and TNF-α." *Id.* Further, he acknowledged that the transient elevation of peripheral monocytes after vaccinations has been observed post-influenza vaccination, but that there "is no evidence to link a transient elevation of peripheral monocyte count with nausea and vomiting." *Id.* at 4.

In his second report, Dr. He stated that the "published data" demonstrates that aged adults have a much-weakened immune response to the influenza vaccine. Resp. Ex. C at 3. During the hearing Dr. He argued that the *Panda* article, submitted by petitioner, demonstrates that older individuals have dysregulation of cytokine production that may weaken older adults' immune responses to the flu vaccine. Tr. 127-29. He testified that the *Panda* article shows that older adults have higher baseline levels of cytokines, but when stimulated by the inactivated flu vaccine, had a lower cytokine production compared to younger adults. Tr. 129. Dr. He argued that petitioner had a "very weakened immune system" when vaccinated and "it is highly expected to have a reduced immune response." Tr. 130. Dr. He conceded that the *Panda* article compared younger and older adults' immune responses to the *standard* flu vaccine, not the high-dose flu vaccine. Tr. 130. He further conceded that the "effect of giving a high-dose [flu] vaccine" is to create a stronger response. Tr. 131. He stated that if older adults were given the standard flu vaccine, "it would not work," and agreed that "one would expect to have a stronger immune response [to the high-dose flu vaccine] than is shown [in *Panda*] for the older people compared to the standard dose." Tr. 131.

Dr. He also argued that the *Mohanty* article cited by Dr. Byers shows that "the levels of the two proinflammatory cytokines, IL-6 and TNF-α were not increased in both classic and inflammatory monocytes at day 2 after influenza vaccination in older human subjects." *Id.* at 2. However, Dr. He did not distinguish, as the authors do between "responders" and "non-responders." *See* Pet. Ex. 19 at 4. In *Mohanty*, the authors recognized that there were "responders" to the flu vaccine who had "4-fold increase in HAI titer to any of the three strains in the vaccine." *Id.* The *Mohanty* article states, "At day 2, TNF-α production was also significantly higher in older responders than in older non-responders in classical and inflammatory monocytes." Pet. Ex. 19 at 6. During the hearing, Dr. He also testified that the *Mohanty* article shows that IL-10, the immunosuppressant cytokine, is also elevated. Tr. 135. He testified that in older populations which have weakened immune environment, the IL-10 cytokine "comes up earlier than the impacted cytokines," before IL-6 and TNF-α. *Id.* Yet, as discussed above, the *Mohanty* authors found significant increases in IL-10 levels in older vaccine

non-responders compared to older *responders* at day 28 in classical monocytes and at day 2 in inflammatory monocytes. Pet. Ex. 19 at 7. The authors stated, "These findings indicate that IL-10 levels are increased in monocytes from older subjects, compared with younger subjects, a potential contributing factor to age-associated alterations in influenza vaccine response." *Id*. However, the responders among the older subjects appeared not to experience the same level of early IL-10 activation as the non-responders. Dr. He acknowledged that the *Mohanty* paper was only measuring monocyte production after the standard vaccine, not the high-dose flu vaccine. Tr. 136. He also testified that he would "expect that IL-6 and TNF-α would rise faster in response to the high-dose flu vaccine." Tr. 137.

Dr. He took issue with Dr. Byers use of the phrase "cytokine storm," as a theory, arguing that a "cytokine release syndrome" is a different entity than what was evident in this case. Resp. Ex. A at 4. He testified that a cytokine storm is a "massive activation of T-lymphocytes…that release a lot of cytokines, causing a cytokine storm." Tr. 139-40. In his first report, Dr. He stated that a cytokine release syndrome (which would be the result of a cytokine storm) "is an acute systemic inflammatory syndrome characterized by fever and multiple organ dysfunction." Resp. Ex. A at 4. During the hearing, he testified that the influenza vaccination has a very gradual process of T-cell activation. Tr. 139. He stated, "the vaccine will be taken up by…antigen presenting cells, those are myeloid cells, dendritic cells, macrophages, which are derived from monocytes. Those cells will migrate to the local lymph nodes, and once inside the lymph nodes they will stimulate the T-lymphocytes." *Id*. Dr. He argued that the *Chatziandreou* article, referenced by Dr. Byers, does not actually demonstrate a "cytokine storm," response to an influenza vaccination, but instead shows a normal immune response to vaccination. Tr. 141. Dr. He is correct that the authors of *Chatziandreou* were not demonstrating a "cytokine storm," but instead examining how "lymph node macrophages initiate an inflammatory response that leads to the activation CD11b lymph node dendritic cells through IL-1α mediated process, which is essential for the elicitation of the humoral response against influenza vaccination." Pet. Ex. 23 at 3. As Dr. He testified, the authors of *Chatziandreou* were able to demonstrate that certain cytokine production peaks at 12 hours post-vaccination. Tr. 141; *see also* Pet. Ex. 23 at 3. The article does not suggest that the vaccine trigged a cytokine release syndrome, but rather the authors were attempting to express that the vaccine begins an inflammatory cascade which is necessary for the initiation of the adaptive immune response. *See* Pet. Ex. 23 at 5.

The Court asked Dr. He to consider whether the normal innate immune response to the vaccine, being the elevation of cytokines, could cause nausea and vomiting. Tr. 141. Dr. He responded that the high-dose flu vaccine could cause common side effects, such as headache, fever, malaise, and nausea. Tr. 145. However, he argued that if petitioner had those symptoms "immediately after vaccination, that's certainly likely" that it was caused by the vaccination. Tr. 149. Dr. He then testified that if petitioner's symptoms occurred within one hour, it would have been caused by something other than the immune system's response to the vaccine, but a neuroreaction. Tr. 149. Dr. He acknowledged that petitioner's monocytes were elevated two days post-vaccination, but opined that "there's no evidence that [the monocyte elevation] is what caused the nausea." Tr. 152. Dr. He was asked by the Court whether it would be reasonable to conclude that petitioner likely had elevated pro-inflammatory cytokines two-days post-vaccination and Dr. He responded, "yeah they might be systemic." Tr. 152.

Dr. He argued that the high-dose flu vaccine does not cause "a more severe adverse event," compared to the standard flu vaccine. Resp. Ex. C at 3. He explained that "the purpose of the increased antigen dose is to enhance immune responses in aged population due to their weakened immune system." *Id.* He stated, "….two large scale studies have unequivocally demonstrated that Fluzone High-Dose provided better protection than regular Fluzone against influenza illness in aged population. However, the adverse events in both high-and regular dose group occurred at similar levels." *Id.*

Dr. He concluded his testimony and expert reports by stating that it was his opinion that there is "no reliable evidence to support Dr. Byers' theory that the influenza vaccine had caused retching and subsequent vasovagal faints in petitioner." *See* Resp. Ex. A, C, & D.

B. Analysis and conclusion of vaccine causation

1. *Althen* prong one

Under *Althen* prong one, the causation theory must relate to the injury alleged. Thus, a petitioner must provide a "reputable" medical or scientific explanation, demonstrating that the vaccine received *can cause* the type of injury alleged. *Pafford*, 451 F.3d at 1355-56. The theory must be based on a "sound and reliable medical or scientific explanation." *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 548 (Fed. Cir. 1994). It must only be "legally probable, not medically or scientifically certain." *Id.* at 549. However, the theory still must be based on a "sound and reliable medical or scientific explanation." *Knudsen* at 548. The Federal Circuit explained in *Althen* that "while [that petitioner's claim] involves the possible link between [tetanus toxoid] vaccination and central nervous system injury, *a sequence hitherto unproven in medicine*, the purpose of the Vaccine Act's preponderance standard is to allow the finding of causation in a field *bereft of complete and direct proof of how vaccines affect the human body.*" *Althen*, 418 F.3d at 1280 (emphasis added).

For the reasons set forth below, I find that petitioner has provided preponderant evidence of a sound and reliable theory to explain how the high-dose influenza vaccine can, within hours of vaccination, cause nausea, vomiting, and malaise, with continuous nausea and vomiting leading to a syncopal event two-days post-vaccination, and therefore petitioner has satisfied *Althen* prong one.

The high-dose influenza vaccine, as explained by both experts in this case, was formulated for people 65 years and older due to poor antibody response to the standard flu vaccine in many older people. Tr. 69, 129. As explained in the *Gravenstein* article, "Immune responses to influenza vaccines decline with age, reducing clinical effectiveness." Resp. Ex. C, Tab 3 at 1.[10] The high-dose flu vaccine contains four times more antigen than the standard dose vaccine. *Id.* at 1; Tr. 69. According to the article by *DiazGranados*, the high dose influenza vaccine improves antibody response to influenza among adults 65 year of age or older. Resp. Ex. C, Tab 2 at 1. Further, the antibody mean titers and seroprotection rates 28 days post-

[10] Gravenstein, S. et al., *Comparative effectiveness of high-dose versus standard-dose influenza vaccination on numbers of US nursing home residents admitted to hospital: a cluster-randomized trial*, 5 Lancet Respir Med, 738-46 (2017). [Resp. Ex. C, Tab 3].

vaccination were significantly higher for those who received the high-dose flu vaccine compared to the standard vaccine. *Id*. at 6.

As explained by Dr. He during the hearing, after vaccination antigen presenting cells take up the flu vaccine antigens and carry them to lymph nodes where toll like receptors stimulate the production of antibodies and inflammatory cytokines. Tr. 142. Dr. Byers opined that the inflammatory cytokines activated by the high-dose influenza vaccine, which contains four times the antigen compared to the standard dose, led to the onset of petitioner's nausea, malaise, and vomiting close in time to the vaccination and then remained elevated for a period of two-days, ultimately leading to his syncopal event on September 8, 2016.

I agree with Dr. He's assessment that petitioner did not have a "cytokine release syndrome," or a "cytokine storm," which was described in the *Lee* article as a "non-antigen specific toxicity that occurs as a result of high-level immune activation." *See* Pet. Ex. 15 at 2. However, Dr. Byers was not using the phrase "cytokine storm" to imply that petitioner's cytokine activity was so severe that it caused petitioner "multiple organ dysfunction," as described in the *Porter* article submitted by respondent. *See* Resp. Ex. A, Tab 1 at 1; Tr. 72. Instead, Dr. Byers explained that use of the phrase "cytokine storm," was used as a nomenclature to describe the upregulation of production of cytokines after vaccination. Tr. 71-72. It is the upregulation of cytokines post-vaccination, in Dr. Byers's opinion, can cause nausea, malaise, and vomiting.

The authors of the *Chatziandreou* article, exploring the inflammatory response to the influenza vaccine, described the activation of cytokines by the lymph node macrophages as a "cytokine storm." Pet. Ex. 23 at 1. *Chatziandreou* explained that macrophages are part of the innate immune system that act as antigen present cells and stated that, "lymph node macrophages initiate an inflammatory response that leads to the activation of CD11b+ lymph node dendritic cells through IL-1α-mediated process, which is essential for the elicitation of the humoral response against influenza vaccine." *Id*. at 3. The authors found that after influenza vaccination, the lymph node macrophages initiate an inflammatory cascade. *Id*. at 5. *Chatziandreou* found that there was a "rapid and significant secretion of IL-1α and IFN-β (cytokines) in the lymph node within he first 90 minutes post-vaccination." *Id*. Further, the authors explained that "levels of acute-phase cytokines MIG, IP-10, KC, MCP-1, MIP-1α, and MIP-1β peaked at 12 hours [post-vaccination], followed by an abrupt decrease by 24 hours post-vaccination." *Id*. at 5. Thus, the *Chatziandreou* article supports Dr. Byers's opinion that the influenza vaccine can rapidly upregulate cytokines and that the use of the phrase "cytokine storm" is found in medical literature outside of those focused solely on cytokine release syndrome.

Dr. He argued that that the *Chatziandreou* article showed a normal response to a vaccine, and that it did not demonstrate that cytokines could remain elevated past 24-hours, thus cytokines could not be responsible for petitioner's continued illness two-days post-vaccination. Tr. 141. However, the article by *Weiner*, submitted by respondent, demonstrated that monocyte (which are pro-inflammatory cells that induce cytokines) levels peak two-to-three days after the high-dose flu vaccine is administered. *See* Resp. Ex. D, Tab 3 at 17. The study by *Weiner* examined inflammatory responses to different vaccines including a standard influenza vaccine and an adjuvanted influenza vaccine. *Id*. at 1. The study demonstrated the most quantitatively

prominent immune response was generated by the adjuvanted influenza vaccine. However, the authors noted that when comparing the two influenza vaccines: "Notwithstanding the evident quantitative differences in transcriptomic responses, the signatures of these responses were qualitatively similar for both vaccines (the adjuvanted and non-adjuvanted influenza vaccines) These signatures were characterized by a sharp peak around Day 1, when monocytes and neutrophil counts increased, and a prominent role for genes associated with early IFN signaling as well as for antigen processing and presentation-related genes." Resp. Ex. C, Tab 5 at 9.

Dr. He testified that the symptoms of nausea, lightheadedness, diaphoresis, and/or pallor are described as symptoms that occur prior to a vasovagal syncope event but occur within one hour of vaccination. Tr. 146; *see also* 42 U.S.C. § 300aa-14(b). Dr. He asserted that these symptoms are caused by an entirely different neuroreaction and not an immune reaction. Tr. 149. Dr. He opined that for "systemic adverse" symptoms to occur, such as headache, fever, or nausea "a lot of cytokines" would be needed. Tr. 142.

I agree with Dr. He that vasovagal syncope as described in Qualifications and Aids to Interpretation, which accompanies the Vaccine Injury Table, may occur through a different mechanism. However, this case does not involve a Table claim for vasovagal syncope. Instead, the petitioner is alleging that he suffered a syncopal event after enduring two-days of sickness, that included nausea, vomiting, fever, and malaise caused by the high-dose influenza vaccine. These symptoms, which petitioner experienced, are identified as common "systemic adverse events" post-vaccination described on the Fluzone High-Dose package insert and on the Centers for Disease Control and Prevention's Flu Vaccine Safety Fact Sheet.

The package insert provides that "myalgia, malaise, headache, and fever (greater than 99.5 degrees F)" are systemic adverse events where "[o]nset was usually within the first 3 days after vaccination and most of the reactions resolved within 3 days." Pet. Ex. 9 at 5. Further, the package insert states that, "Solicited injection-site reactions and systemic adverse events were more frequent after vaccination with the Fluzone High-Dose compared to Fluzone (standard)." *Id.* Additionally, post-marketing reporting of adverse events for the standard Fluzone vaccine included "gastrointestinal disorders: vomiting" and for the high-dose flu vaccine the "gastrointestinal disorders" reported included nausea and diarrhea. *Id.* at 8. The CDC's Flu Vaccine Safety Information Fact Sheet also provides that "common side effects from the flu shot include: headache, fever, nausea, and muscle aches." Pet. Ex. 16 at 1. Further, the fact sheet states that these listed side effects "are generally mild and go away on their own *within a few days." Id.*

Furthermore, Dr. He conceded that the package insert identified these systemic adverse events but asserted that "a lot of cytokines" would be necessary to induce such symptoms. *See* Tr. 142, 152. As discussed above, the *Chatziandreou* articles demonstrate that the influenza can rapidly upregulate cytokines and the cytokine activity remains elevated for a period of two to three days post-vaccination. Dr. He argued that the *Mohanty* article demonstrates that cytokine production in older adults' post-influenza vaccine is blunted by anti-inflammatory cytokines, such as IL-10, and it is evidence that Dr. Byers's theory that a rapid and prolonged cytokine production would be responsible for such systemic symptoms as headache, fever, nausea, or

vomiting is unsupported by the medical literature. Dr. He's reliance on *Mohanty* for this proposition is misplaced.

First, the *Mohanty* researchers were comparing inflammatory responses to the standard influenza vaccine between younger and older adults and did not evaluate the inflammatory response in older adults who received the high-dose flu vaccine. Even the authors at the end of their paper wrote, "It will be of interest to determine whether the impaired activation of IL-6 and TNF-α expression….are affected by high-dose or adjuvanted influenza vaccines." Pet. Ex. 19 at 11. Second, the *Mohanty* article shows that inflammatory responses to the standard flu vaccine is reduced in *some* older adults, which can lead to a reduction in antibody response, necessitating the need for a different, stronger vaccine for older populations such as the high-dose influenza vaccine that petitioner received. However, *Mohanty* also found that some older adults, deemed "responders," did have increased levels of TNF-α and IL-6 monocytes at day 2, 7 and 28 after receiving the standard flu vaccine. I agree with Dr. Byers that petitioner would likely fall into the category of "responder" in the *Mohanty* article, as he clearly demonstrated an immune response to the high-dose flu vaccine.

Lastly, Dr. He argued that petitioner had not submitted any articles that a normal response to a vaccine, influenza or other, could result in nausea and vomiting. Tr. 121. However, when asked by the Court if a study would be conducted to do a study on "transient symptoms like nausea or vomiting or fever or headache that goes away in two or three days," Dr. He responded that it would be a "difficult study…because by the time [a person] goes to the doctor, [they] are already self-cured," and that "the National Institutes of Health will not fund it because they say that's a minor issue." *Id.* at 122. Given that the CDC Fact Sheet and the FDA approved package insert clearly report such symptoms as common, it seems unnecessary to undertake an epidemiological study to demonstrate such immune responses to cause those types of symptoms. Furthermore, as the *Weiner* study explained that there was high subject variability on the transcriptomic and reactogenicity measured in the study to the two different flu vaccines, indicates that symptoms such as nausea, vomiting, and gastrointestinal illness are common and occur in a minority of recipients of vaccines. *See* Resp. Ex. C, Tab 5 (observing that there were adverse events recorded after administration of all the vaccines administered in the study). The authors of *Weiner* also hypothesized that the differences in reactions to the flu vaccines could be explained by prior infection or vaccination with similar matching strains of the influenza vaccine. It seems highly likely that an eighty-year-old adult, such as the petitioner, would be likely to have prior exposure to similar influenza strains either by infection and/or vaccination. While Dr. He repeatedly stated that it would take "a lot of cytokines" to cause the type of illness that petitioner experienced in the wake of the vaccination, Dr. He cited no evidence for that proposition. Instead, it appears that the high-dose flu vaccine generated a strong inflammatory response, as both Drs. He and Byers indicated was the purpose of the high-dose flu vaccine in older adults to boost antibody production, and that petitioner suffered common post-vaccination symptoms as described by the CDC and the package insert.

Importantly, requiring epidemiologic studies to prove causation "impermissibly raises a claimant's burden under the Vaccine Act." *Capizzano*, 440 F.3d 1317, 1326. As the Federal Circuit observed, "As a general matter, epidemiological studies are designed to reveal statistical trends only for a carefully constructed test group. Such studies provide no evidence pertinent to

persons not within the parameters of the test group." *Moberly*, 592 F.3d 1315, 1324. Petitioner's need to provide a medical theory of causation that needs to be corroborated by medical literature *or* epidemiological evidence. *Knudsen*, 35 F3d. at 548 (emphasis added). Here, petitioner has provided a medical theory of causation that has been corroborated by medical literature, including the high-dose flu vaccine package insert and the CDC's Flu Vaccine Safety Sheet, which show that the vaccine *can cause* nausea, vomiting, headache and fever-systemic adverse events post-vaccination and that those systemic adverse events can occur within a three-day time period post-vaccination. As such, petitioner has satisfied *Althen* prong one.

2. *Althen* prong two

Under *Althen* prong two, petitioner must prove by a preponderance of the evidence that there is a "logical sequence of cause and effect showing that the vaccination was the reason for the injury. *Capizzano*, 440 F.3d at 1324 (quoting *Althen*, 418 F.3d at 1278). "Petitioner must show that the vaccine was the "but for" cause of the harm or in other words, that the vaccine was the reason for the injury.'" *Pafford*, 451 F.3d at 1356 (internal citations omitted).

In evaluating whether this prong is satisfied, the opinions and views of the vaccinee's treating physicians are entitled to some weight. *Andreu*, 569 F.3d at 1367; *Capizzano*, 440 F. 3d at 1326 ("[M]edical records and medical opinion testimony are favored in vaccine cases, as treating physicians are likely to be in the best position to determine whether a 'logical sequence of cause and effect show[s] that the vaccination was the reason for the injury.'" (quoting *Althen*, 418 F.3d at 1280)). The petitioner need not make a specific type of evidentiary showing, i.e., "epidemioligc studies, rechallenge, the presence of pathological markers or genetic predisposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect." *Capizzano*, 440 F.3d at 1325. Instead, petitioner may satisfy his burden by presenting circumstantial evidence and reliable medical opinions. *Id*. at 1325-26.

I find that petitioner has provided preponderant evidence of a logical sequence of cause and effect. This finding is based on expert opinion, statements by petitioner's treating physician, his clinical course, and the lack of evidence to support an alternative cause.

Petitioner's expert, Dr. Byers, opined that petitioner's nausea, malaise, and vomiting, which began shortly after the high-dose flu vaccination, was caused by a release of pro-inflammatory cytokines that remained elevated for two days, resulting in his vasovagal event, ultimately leading to his fall and subsequent injuries. Dr. Byers observed that Flu Vaccine Safety Information provided by the CDC provides that "nausea" "headache" and, "fever," are all side effects that the CDC states are "common." Pet. Ex. 21 at 2; *see also* Pet. Ex. 16. Additionally, Dr. Byers referenced the Fluzone High-Dose package insert which provides a summary of post-injection reactions within seven days of vaccination, which included "malaise," "headache," and "fever," as "systemic adverse events." Tr. 98; *see also* Pet. Ex. 9 at 5. The package insert states that, "Onset was usually within the first 3 days after vaccination and a majority of the reactions resolved within 3 days." Pet. Ex. 9 at 5. Further, the package insert provides that "nausea and diarrhea," have been reported as a side-effect in the post-approval use

of Fluzone High-Dose. Pet. Ex. 9 at 8. Dr. Byers explained that petitioner's onset of his nausea and malaise later in the day after receipt of the vaccine was consistent with the package insert's description of both systemic adverse events following the vaccination and the post-marketing reports of nausea. During the hearing, Dr. He also conceded that the "most common side effects listed on the vaccine package insert…include headache, fever, malaise, and nausea," all which were present in petitioner in the two days after he received the high-dose flu vaccine. Tr. 145. Dr. He stated that those symptoms were generally accepted as side effects and that petitioner's response to the flu vaccine was a "normal reaction," to the high-dose flu vaccine. Tr. 152.

Petitioner's medical records reflect that the onset of his nausea and malaise began the same evening he received the high-dose flu vaccine. On September 8, 2016, two days after petitioner received the influenza vaccine, an ambulance was called to his house, responding to petitioner has "fallen out of his wheelchair, striking his head on the toilet." Pet. Ex. 3 at 1. According to the ambulance summary, "petitioner reported that he and his wife went to get a flu shot yesterday, and that his nausea started after he was given the shot. He…got up to go to the bathroom….after he got back into his wheelchair he began to wretch really hard, passing out, and waking up on the floor." *Id*. While in the hospital, cardiologist, Dr. Naginder Sharma was requested to examine the petitioner and clear him for his left shoulder surgery. Pet. Ex. 4 at 168. Dr. Naginder Sharma recorded petitioner's history of present illness and wrote:

> The patient and his wife, this Tuesday, had a flu shot. They felt very unwell and the patient was very nauseous all day. On the morning of admission, the patient felt sick….He started having nausea and then started retching very hard. Because of that he fell forward and hit his head and there was a laceration over the left forehead…He did complain of left shoulder pain at that time, but no x-rays were obtained. As he was being loaded into the car, the had a seizure with rolling of the eyes upwards. He was then brought back to the emergency room where he had another seizure and therefore he was admitted. He also underwent left shoulder x-ray which showed fracture dislocation of the proximal left humerus.

Id.

Furthermore, when petitioner was first admitted to the hospital on September 8, 2016, his blood work showed that his monocyte level was elevated to 13.3%, which later decreased to 5.0% by his discharge date on September 13, 2016. Pet. Ex. 4 at 150, 263. Both Dr. Byers and Dr. He agreed that monocytes are part of the innate immune system which respond to vaccine stimulation and that monocytes are necessary for stimulating proinflammatory cytokines. *See* Tr. 90, 124. Dr. Byers stated that the monocytes were induced by the vaccine, which would mean an increase in the production of inflammatory cytokines. Tr. 91, 92. Dr. He agreed with Dr. Byers that the documented elevation in petitioner's monocytes was evidence that the vaccine activated petitioner's innate immune system. Resp. Ex. C at 4. The *Mohanty* article supports Dr. Byers's opinion that monocytes in "older responder" populations to the flu vaccine would have increased proinflammatory levels two days post-vaccination. *Mohanty* states that, "At day 2, TNF-α production was also significantly higher in older responders than in nonresponses in classical and inflammatory monocytes." Pet. Ex. 19 at 6.

While the *Mohanty* article was studying the inflammatory response to the standard influenza vaccine, both Drs. He and Byers acknowledged that older populations generally had a lower adaptive immune response to the standard vaccine, which is why the high-dose flu vaccine was developed. Dr. He stated that the "aged population [has] a much-reduced immune response, weaker response," to the standard influenza vaccine and the purpose of the high-dose influenza vaccine was to generate a "stronger response" in older people. Tr. 129,131. Dr. He acknowledged that the petitioner would have had "a stronger immune response" than what was being shown in the *Mohanty* paper because he received the high-dose influenza vaccine, as opposed to the standard flu vaccine which was the subject of the paper. Tr. 131. Dr. He suggested that the "normal" response to the high-dose vaccine could include systemically elevated pro-inflammatory cytokines, which would result in a headache, fatigue, and nausea.

Finally, petitioner's primary care physician also associated petitioner's nausea and vomiting, which led to his syncope event to the flu vaccine petitioner received on September 6, 2016. The medical record from petitioner's appointment with Dr. Bates on October 11, 2016 states:

> Pt fell and hit his head-superficial injury to head and [left] shoulder injury needing total left shoulder replacement, fracture of left hip with osteopenia, pt went to ER on 09/08/2016 for fall, pt passed out and hit his head, pt had flu shot previously.

Pet. Ex. 2 at 89. During the hearing, Dr. Bates testified that it was petitioner's light-headedness or faintness that made him fall. Tr. 52. He stated that it was his opinion that the flu shot petitioner received was the cause of petitioner's fainting or syncopal event. *Id*. He stated that the onset of petitioner's nausea and vomiting after the high-dose flu vaccine was "not unusual," and that it can begin a few hours after vaccination and last for two to three days. Tr. 53. When the Court asked Dr. Bates whether he thought petitioner's syncopal event or fainting was directly caused by the nausea and retching petitioner had been experiencing, he responded, "I do." Tr. 58.

In this case, petitioner experienced malaise, nausea, vomiting, and an elevated temperature after receiving the high-dose influenza vaccine. Additionally, as noted above, petitioner's monocytes were elevated when he was admitted to the hospital on September 8, 2016, two-days post vaccination, which is consistent with the *Mohanty* and *Weiner* articles indicating that pro-inflammatory cytokines post-flu vaccination remain elevated for a period of two to three days. Because of petitioner's continued nausea, retching and malaise, he suffered a vasovagal event in which he hit his head and fractured his shoulder, necessitating a reverse total shoulder replacement surgery. As such, petitioner has demonstrated that the high-dose influenza *did* cause his injury, consistent with the theory presented by Dr. Byers in *Althen* prong one. *Althen* prong two is satisfied.

3. *Althen* prong three

Althen prong three requires petitioner to establish a "proximate temporal relationship" between the vaccination and the injury alleged. *Althen*, at 1281. That term has been defined as "medically acceptable temporal relationship." *Id*. The petitioner must offer "preponderant proof

that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disease's etiology, it is medically acceptable to infer causation-in-fact." *De Bazen*, 539 F.3d at 1352. The explanation for what is a medically acceptable time frame must also coincide with the theory of how the relevant vaccine can cause the injury alleged (due to *Althen* prong one). *Id.*; *Koehn v. Sec'y of Health & Human Servs.,* 773 F.3d 1239, 1243 (Fed. Cir. 2014); *Shapiro v. Sec'y of Health & Human Servs.*, 101 Fed. Cl. 532, 542 (2011), *recons. denied after remand*, 105 Fed. Cl. 353 (2021), *aff'd mem.,* 503 F. App'x 952 (Fed. Cir. 2013).

Prior to the vaccination on September 6, 2016 petitioner was in his normal state of health. Petitioner stated that the evening following receipt of the high-dose flu vaccine, he began to feel ill. *See* Pet. Ex 17 at ¶ 2; Tr. 9. Petitioner's statements are corroborated by the medical records. Two days following the vaccination, petitioner continued to experience nausea, fatigue, malaise and vomiting, resulting in a syncope event that led to him falling and breaking his shoulder. On September 8, 2016, emergency services were called to petitioner's house, where they recorded that petitioner's "nausea started after he was given the shot." Pet. Ex. 3 at 1. While at the emergency department, under "GI Symptoms," a nursing note indicated, "Has been nauseated after getting the flu shot 2 days ago." Pet. Ex. 4 at 600. During petitioner's hospital admission, petitioner was seen by Dr. Bala Grandhi for adrenal insufficiency and hypothyroidism, where again petitioner reported that he "had a flu shot after which he started feeling very sick and nauseated. Then he fell and started bleeding from his head." *Id.* at 166. When petitioner was getting cleared for his left shoulder surgery, Dr. Sharma wrote, "The patient and his wife…had a flu shot. They felt unwell and the patient was very nauseous all day. On the morning of admission, the patient felt sick." *Id.* at 148.

Dr. Byers opined that the onset of petitioner's symptoms of nausea, vomiting, fatigue and malaise are consistent with an immune response to the high-dose influenza vaccination. Tr. 98. The package insert for the Fluzone High-Dose explains that certain systemic adverse reactions, such as malaise, headache, and fever occur "within the first 3 days after vaccination." Pet. Ex. 9 at 5. Additionally, the Flu Vaccine Safety Information fact sheet created by the CDC, lists nausea, headache, fever and muscle aches as "common side effects" from the flu shot and also indicate that these symptoms "go away on their own within a few days," suggesting that the onset of these symptoms is close in time to receipt of the vaccination. *See* Pet. Ex. 16 at 1. Dr. Byers opined that the high-dose flu vaccine triggered an upregulation of cytokines which remained elevated for a period of two days, resulting in systemic adverse symptoms such as nausea, vomiting, and malaise.

Dr. He argued that the onset of petitioner's symptoms, if they occurred within one hour of vaccination, was not caused by an immune reaction, but instead a possible "neuroreaction." Tr. 149. However, Dr. He conceded that symptoms such as headache, fatigue, malaise, and nausea are also common adverse reactions identified on the Fluzone Package insert. *See* Tr. 145. Further, petitioner's symptoms did not resolve after a short period of time but remained consistent for at least two-days post-vaccination, more consistent with an immune reaction to the high-dose flu vaccination than a transient "neuroreaction," that could have resulted in a vasovagal syncope event closer in time to the vaccination. Finally, the onset of petitioner's nausea, malaise, and vomiting was consistent with the onset of symptoms described in the Fluzone High-Dose package insert and the CDC's Flu Vaccine Safety sheet.

Thus, the onset of petitioner's symptoms beginning the same evening of the vaccination and continuing for two-days is consistent with the theory proposed by Dr. Byers and petitioner has demonstrated *Althen* prong three by preponderant evidence.

IV. Conclusion

In accordance with the above, petitioner has established by preponderant evidence that he is entitled to compensation, demonstrating that the high-dose flu vaccine administered on September 6, 2016, was the cause-in-fact of his syncope event leading to his left shoulder injury. A separate ruling on damages will be issued.

IT IS SO ORDERED.

s/Thomas L. Gowen
Thomas L. Gowen
Special Master